Cover sheet

Title

Insecticide-treated bed nets and curtains for preventing malaria

Reviewers

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Christian Lengeler is the sole contributor.

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Potential conflict of interest

None known.

What's new

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This is a major update with a revision of the text, tables, and results.

- An additional 16 trials have been identified and reviewed, of which 4 were included.
- The sensitivity analysis (with group 2 trials) has been removed to clarify the main results.
- The literature in all sections and especially background and discussion has been updated.
- Overall mortality results have been entered with the reverse variance function in order to present confidence intervals adjusted for clustering.

Dates

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Synopsis

Insecticide-treated nets can reduce deaths in children by one fifth and episodes of malaria by half.

Sleeping under mosquito nets treated with insecticide aims to prevent malaria in areas where the infection is common. They are widely promoted by international agencies and governments to reduce the bad effects of malaria on health. This review showed that good quality studies of impregnated nets markedly reduce child deaths and illnesses from malaria.

Abstract

Background
Malaria is an important cause of illness and death in many parts of the world, especially in sub-Saharan Africa. There has been a renewed emphasis on preventive measures at community and individual levels. Insecticide-treated nets (ITNs) are the most prominent malaria preventive measure for large-scale deployment in highly endemic areas.

Objectives
To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates.

Search strategy
I searched the Cochrane Infectious Diseases Group trials register (January 2003), CENTRAL (*The Cochrane Library*, Issue 1, 2003), MEDLINE (1966 to October 2003), EMBASE (1974 to November 2002), LILACS (1982 to January 2003), and reference lists of reviews, books, and trials. I handsearched journals, contacted researchers, funding agencies, and net and insecticide manufacturers.

Selection criteria
Individual and cluster randomized controlled trials of insecticide-treated bed nets or curtains compared to nets without insecticide or no nets. Trials including only pregnant women were excluded.

Data collection & analysis
The reviewer and two independent assessors reviewed trials for inclusion. The reviewer assessed trial methodological quality and extracted and analysed data.

Main results
Fourteen cluster randomized and eight individually randomized controlled trials met the inclusion criteria. Five trials measured child mortality: ITNs provided 17% protective efficacy (PE) compared to no nets (relative rate 0.83, 95% confidence interval (CI) 0.76 to 0.90), and 23% PE compared to untreated nets (relative rate 0.77, 95% CI 0.63 to 0.95). About 5.5 lives (95% CI 3.39 to 7.67) can be saved each year for every 1000 children protected with ITNs. In areas with stable malaria, ITNs reduced the incidence of uncomplicated malarial episodes in areas of stable malaria by 50% compared to no nets, and 39% compared to untreated nets; and in areas of unstable malaria: by 62% for compared to no nets and 43% compared to untreated nets for *Plasmodium falciparum* episodes, and by 52% compared to no nets and 11% compared to untreated nets for *P. vivax* episodes. When compared to no nets and in areas of stable malaria, ITNs also had an impact on severe malaria (45% PE, 95% CI 20 to 63), parasite prevalence (13% PE), high parasitaemia (29% PE), splenomegaly (30% PE), and their use improved the average haemoglobin level in children by 1.7% packed cell volume.

Reviewers' conclusions
ITNs are highly effective in reducing childhood mortality and morbidity from malaria. Widespread access to ITNs is currently being advocated by Roll Back Malaria, but universal deployment will require major financial, technical, and operational inputs.

Background

Malaria remains a major public health problem. Global estimates of the malaria disease burden for 2000 indicated that there were at least 300 to 500 million clinical cases annually, of which 90% occurred in sub-Saharan Africa. Moreover, around one million deaths are related to malaria every year, of which an overwhelming proportion occurs in Africa (WHO 1997; WHO 2003). In Africa, malaria accounts for an estimated 25% of all childhood mortality below age five, excluding neonatal mortality (WHO 2003). Recent studies suggest that this percentage might even be higher because of the contribution of malaria as indirect cause of death (Alonso 1991; Molineaux 1997). In addition, it might be more of a problem in adults than thought previously, as suggested by the high proportion of adults dying of "acute febrile illness" in Tanzania (Kitange 1996). In Africa, malaria is the primary cause of disease burden measured by disability-adjusted life years (WHO 2003; World Bank 1993). In countries outside the African continent, malaria appears to be an increasing problem; for example, in India malaria is making a comeback after decades of effective control. Malaria places an enormous economic burden on affected countries and has a highly detrimental effect on economic and social development.

In 1992, the World Health Organization convened a ministerial conference in Amsterdam to give a new impetus to control activities. While the consensus at this meeting was that prompt access to diagnosis and treatment remained the mainstay of malaria control, there was a renewed emphasis on preventive measures, both at the community and at the individual level (WHO 1993). The most promising preventive measures mentioned were insecticide-treated bed nets and curtains, collectively known as insecticide-treated nets (ITNs). In 1998, the main international health agencies launched an ambitious partnership, Roll Back Malaria, to tackle the global malaria issue. The wide-scale implementation of ITNs is now one of the four main strategies to reduce morbidity and mortality from malaria (WHO 2003), with a target set by African Heads of State to protect 60% of all pregnant women and children by 2005. As a result, many large-scale programmes have taken off during the last few years.

Insecticide-treated nets (ITNs)

Using mosquito nets as a protection against nuisance insects was practiced in historical times (Lindsay 1988). During World War II, Russian, German, and US armies treated bed nets and combat fatigues with residual insecticide to protect soldiers against vector-borne diseases (mainly malaria and leishmaniasis) (Curtis 1991). In the late 1970s, entomologists started using synthetic pyrethroids: their high insecticidal activity and low mammalian toxicity made them ideal for this purpose.

In the 1980s, studies of ITNs showed that pyrethroids were safe and that ITNs had an impact on various measures of mosquito biting (such as the proportion of mosquitoes successfully feeding on humans and the number of times a mosquito bit humans in one night). These studies showed that pyrethroids worked by both repelling and killing mosquitoes. In addition, researchers determined optimal doses of various insecticides with different materials (Curtis 1991; Curtis 1992a; Curtis 1996; Lines 1996; Rozendaal 1989a). The cost-effectiveness of ITNs has also been demonstrated (Goodman 1999; Hanson 2003).

Given the part played by *Plasmodium falciparum* malaria as a direct and indirect cause of death in African children, the main public health question for ITNs is whether they reduce mortality in children. One observational study of impregnated bed nets in The Gambia reported a 42% reduction in all mortality in children aged 1 to 59 months in 1991 (Alonso 1991). This dramatic result from the first mortality trial prompted the UNDP/World Bank/WHO Special Programme for

Research and Training in Tropical Diseases (TDR) to collaborate with around 20 agencies to launch four additional large-scale trials to measure the impact of ITNs on overall child mortality in different endemic areas of Africa (Burkina Faso, The Gambia, Ghana, and Kenya). Since this time, several trials have been conducted including a large-scale trial completed in 2000 in Western Kenya in an area of high perennial transmission.

Objectives

To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates.

Hypotheses

Any effect of ITNs compared to routine antimalarial control measures in reducing malaria-specific and all-cause morbidity and mortality will be:

- less in areas with high entomological inoculation rates (ie stable malarious areas with > 1 infective bite per year) compared to areas with low inoculation rates (unstable malaria with < 1 infective bite per year);
- less when the population under study already uses untreated bed nets regularly before the start of the trial (coverage of untreated nets by household at least 40%).

The original protocol aimed to explore whether the impact of ITNs on all-cause mortality is greater in areas where access to treatment for malarial illness is limited. However, I could not investigate this because the relevant measures of treatment access were not available.

Criteria for considering studies for this review

Types of studies

Individual and cluster randomized controlled trials.

Types of participants

Children and adults living in rural and urban malarious areas.

Excluded: trials dealing only with pregnant women, because they are reviewed elsewhere (*see* Ekwaru 2004); and trials examining the impact of ITNs among soldiers or travellers, because they are not representative of the general population.

Types of interventions

Bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose of:

- 200 mg/m^2 permethrin or etofenprox;
- 30 mg/m^2 cyfluthrin;
- 20 mg/m^2 alphacypermethrin;
- 10 mg/m^2 deltamethrin/lambdacyhalothrin.

No distinction was made between insecticide-treated bed nets and door/window/eave/wall curtains, which were assumed to have approximately the same impact.

Recently, other types of materials such as wall curtains, blankets, sheets, and veils have also been treated and assessed. However, these are excluded from the review because they are difficult to compare to treated mosquito nets and curtains for which many more studies are available; they are listed in the 'Characteristic of excluded trials'.

Types of outcome measures

- Child mortality from all causes.

Measured using protective efficacy and rate difference.

- Malaria specific child mortality.

Measured using "verbal autopsy" reports that fulfil standard clinical criteria for a probable malaria death (Snow 1992; Todd 1994).

- Severe disease.

Measured using site-specific definitions, which were based on the World Health Organization guidelines (WHO 1990) and on Marsh 1995. The definition included *P. falciparum* parasitaemia. Cerebral malaria was defined as coma or prostration and/or multiple seizures. The cut-off for severe, life-threatening anaemia was set at 5.1g/litre (WHO 1990).

- Uncomplicated clinical episodes.

Measured using site-specific definitions, including measured or reported fever, with or without parasitological confirmation. Measurements were usually done in the frame of prospective longitudinal studies, but I also considered trials using validated retrospective assessments in the frame of cross-sectional surveys. In areas with entomological inoculation rates below 1 (unstable malaria), I considered *P. falciparum* and *P. vivax* episodes separately.

- Parasite prevalence.

Parasite prevalence due to *P. falciparum* and *P. vivax* was obtained using the site-specific method for estimating parasitaemia – usually thick and/or thin blood smears. When more than one survey was done, the reported prevalence result is the average prevalence of all the surveys.

- High parasitaemia.

Measured using site-specific definitions of high parasitaemia, provided the cut-off value between high and low was determined prior to data analysis.

- Anaemia.

Expressed in mean packed cell volume (PCV); it is equivalent to the percentage haematocrit. Results given in g/decilitre were converted with a standard factor of 3:1, that is, 1 g/decilitre equals 3% PCV (Wallach 1986).

- Splenomegaly.

Measured in all trials using the Hackett scale.

- Anthropometric measures.

Standard anthropological measures (weight-for-age, height-for-age, weight-for-height, skinfold thickness, or mid-upper arm circumference) and the impact of ITNs on them.

Search strategy for identification of studies

I attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

I searched the following databases using the search terms and strategy described in Table 01.

- Cochrane Infectious Diseases Group's trials register (January 2003).
- Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 1, 2003).
- MEDLINE (1966 to October 2003).
- EMBASE (1974 to November 2002).
- LILACS (1982 to January 2003).

Handsearching

I handsearched some foreign language tropical medicine journals (*Bulletin OCEAC*, *Bulletin de la Société de Pathologie Exotique, Médecine Tropicale, Revista do Instituto de Medicina Tropical de Sao Paulo*) for the period 1980 to 1997.

Researchers, organizations, and pharmaceutical companies

I contacted many researchers actively involved in the field of ITNs and asked about unpublished past or ongoing work.

I contacted the following agencies, which have funded ITN trials, for unpublished and ongoing trials: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR); International Development Research Center (IDRC), Canada; The Department for International Development, UK; and The European Union Directorate-General XII.

I contacted the following manufacturers of pyrethroids used for treating netting for unpublished and ongoing trials: AgrEvo (now part of Bayer); Bayer; Cyanamid; Mitsui; Sumitomo; and Zeneca (now part of Syngenta).

Reference lists

I consulted the following reviews: Abdulla 1995; Bermejo 1992; Carnevale 1991; Cattani 1997; Choi 1995; Curtis 1992b; Molineaux 1994; Rozendaal 1989a; Sexton 1994; Voorham 1997; WHO 1989; Xu 1988; Yadav 1997; and Zimmerman 1997.

I consulted the following books dealing with ITNs: 'Control of disease vectors in the community' (Curtis 1991); 'Malaria: waiting for the vaccine' (Targett 1991); and 'Net Gain, a new method for preventing malaria deaths' (Lengeler 1996a; Lengeler 1997a).

I also checked the reference lists of all trials identified by the above methods.

Methods of the review

Study selection

The reviewer and two independent assessors experienced in trial epidemiology (Dr Gerd Antes and Dr Daniel Galandi, German Cochrane Centre) applied the inclusion criteria to all identified trials and reached agreement by consensus.

Assessment of methodological quality

I assessed the methodological quality of the included trials using generation of allocation sequence, allocation concealment, inclusion of all randomized participants, and blinding, as described in Table 02.

Data extraction

I used standard forms to extract the following descriptive data.

- Trial location.
- Duration and type of intervention.
- Randomization procedure.
- Type of control group.
- Co-interventions.
- Age and gender of participants.
- Percentage of target group protected by ITNs and untreated nets.
- Malarial endemicity (as defined by the entomological inoculation rate: the number of times on average a person living in the area receives an infected mosquito bite per year).
- Species and proportion of Plasmodium parasites.
- Main vectors.

When these data were not given in the primary trial reference, I used secondary sources and included the references.

Data analysis

I entered data as numerators and denominators for all dichotomous outcomes. For continuous variables, I entered data as the number of participants, mean, and standard deviation.

I used EasyMA 2001 and Review Manager 4.2.2 to calculate the relative risk, relative rate, rate difference, summary relative risk/rate, summary weighted mean difference, and for testing the homogeneity between trials (using a chi-squared (chi^2) test). Both software packages provided similar results for all outcomes.

I considered only crude rate or risk ratios, that is, not adjusted for any co-variates. If only adjusted rates were given in a reference, I attempted to contact the authors to provide the crude rates/risks.

Many trials in the area of vector control interventions are randomized by cluster. While the actual rate/risk ratio is not affected by cluster allocation, the confidence interval (CI) has to be adjusted (made wider) to take into account the inter-cluster variability. This problem has been reviewed by several authors (Bennett 2002; Donner 1993; Donner 1994; Hayes 2000; Klar 1995). This presented me with the problem of interpreting the statistical significance of trials that had not corrected for design effects in their calculations of confidence intervals, and how to obtain accurate confidence intervals when combining data between such trials. For the child mortality from all causes outcome, corrected confidence intervals were available, and I used the generic inverse variance method available in Review Manager 4.2 to combine cluster randomized controlled trials and obtain corrected confidence intervals. Unfortunately, corrected confidence intervals or standard errors were not available for all trials for the other outcomes. Because of this, I have presented summary relative risks without confidence intervals and in tables, rather than with meta-analysis figures.

For parasite prevalence, I calculated an average denominator from all the surveys and chose the appropriate numerator to fit the average prevalence and average denominator. I selected this procedure in order not to inflate the denominator artificially by adding up the participants from repeated surveys. This procedure gives more weight to larger trials doing only one survey rather than smaller trials doing multiple surveys.

I performed a limited number of additional analyses with the mortality data. I used Epi Info 2002 to perform linear regressions in order to test for trends in the mortality outcomes as a result of transmission intensity. Mortality was measured using protective efficacy and rate difference. Protective efficacy is based on the relative risk or relative rate. The protective efficacy (PE) is calculated as PE = (1 - relative risk or relative rate) x 100. Rate difference estimates directly how many child deaths can be avoided through the use of the intervention (in this case deaths per 1000 children protected per year). I only calculated rate difference for mortality from all causes since it was the only measure for which similar incidence measures were used in all trials.

Comparisons
I pre-specified two comparisons: trials in which the control group did not have a net at all; and trials in which the control group had untreated bed nets or curtain; and pre-specified one stratified analysis: entomological inoculation rate above or below one (stable versus unstable malaria)

Description of studies

Study selection
I identified 113 potentially relevant studies. Of these I excluded 32 published studies without further analysis (and did not include in the 'Characteristics of excluded studies') for the following reasons:

- 15 were only descriptive in nature with no defined control groups, used a before-after evaluation design or a comparison of users versus non-users, and mainly concerned untreated nets (Bradley 1986; Burkot 1990; Campbell 1987; Cattani 1986; Clarke 2001; Dulay 1992; Dutta 1989; Fernandez 1991; Genton 1994; Millen 1986; Rozendaal 1989b; Samarawickrema 1992; Sandy 1992; van der Hoek 1998; Voorham 1997).
- 11 were pragmatic evaluations of ITN programmes with no defined control groups and varying levels of reported use (Barutwanayo 1991; D'Alessandro 1997b; Dapeng 1996; Holtz 2002; Li 1989; McClean 2002; Nguyen 1996; Rowland 1997; Schellenberg 2001; Van Bortel 1996; Xavier 1986).
- 2 were randomized controlled trials that only looked at untreated nets (Nevill 1988; Snow 1988).
- 4 trials only examined the impact of ITNs on pregnant women (Browne 2001; D'Alessandro 1996; Dolan 1993; Shulman 1998).

I identified the remaining 81 trials (including 10 (12%) unpublished trials) through the following sources.

- Electronic sources and manual search of references: 57 (70%).
- Handsearch of journals in non-English language journals: 4 (5%).
- Books and reviews: 2 (3%).
- Insecticide manufacturers: 12 (15%).
- Personal contacts with authors and internet search: 6 (7%).

Of these, 59 trials were excluded: 55 because they were not randomized (in two, allocation was achieved "by chance"); 2 because they used materials other than bed nets or curtains (such as wall curtains or blankets); and 2 because they were not adequately controlled (before and after assessments). I have provided the reasons for excluding them in the 'Characteristics of excluded studies'.

The remaining 22 trials, including 1 trial that is currently unpublished, met the inclusion criteria for this review. These trials are described below (see the 'Characteristics of included studies' for details).

Trial design and location
Fourteen of the included trials were cluster RCTs (by villages, blocks of villages, zones within one village), and 8 were individual RCTs (6 by household and 2 by individuals) (Table 02). The eight individual randomized controlled trials were analysed on an intention-to-treat basis.

Thirteen trials were conducted in sub-Saharan Africa, 5 in Latin America, 2 in Thailand, 1 in Pakistan, and 1 in Iran. Thus 13 trials were carried out in areas of stable endemicity areas, and 9 in areas of unstable endemicity.

Participants
Trials included either the whole population of selected areas (typically in low endemicity areas) or specific age groups (typically children in high endemicity areas), and gender ratios were well balanced (range of male:female ratio: 0.8 to 1.2).

Interventions
Nineteen trials examined the impact of treated bed nets, while two examined the impact of treated curtains. One trial compared treated nets, treated curtains, and no bed nets or curtains (Kenya (Sexton)). In some trials the intervention consisted of treating existing nets with an insecticide ('treatment of nets') while in other trials the investigators provided treated mosquito nets or curtains to the population ('treated nets' and 'treated curtains'). Most nets or curtains were treated with permethrin (200 (n = 3), 500 mg (n = 10), or 1000 mg/m^2 (n = 1)). The remaining nets or curtains were treated with lambdacyhalothrin (10 to 30 mg/m^2, n = 4), deltamethrin (25 mg/m^2 (n = 2), or cyfulthrin (40 mg/m^2, n =1). One study used lambdacyhalothrin (10 mg/m^2) for the first year and permethrin (500 mg/m^2) for the second year (Peru Coast (Kroeger)).

Half of the trials did not use bed nets or curtains as the control group, and other 11 trials used untreated nets or curtains. The usage rate of the untreated nets was high (> 80%), except in Gambia (D'Alessand), in which it varied between 50% and 90% (according to the area) in both the intervention and control groups, and in Peru Coast (Kroeger) in which it was 63%; no usage rate provided for Madagascar(Rabariso).

Outcomes
The five trials that examined child mortality from all causes as an outcome were conducted in highly malaria endemic areas in sub-Saharan Africa. No trial presented results for all the possible outcomes, and the majority of trials presented two to five different outcomes (*see* Table 02).

Methodological quality of included studies
See Figure 01 for a summary of the methodological quality of the included trials.

Generation of allocation sequence
Generation of the allocation sequences used random number tables or an equivalent method in 9 trials (graded 'A'); randomization was mentioned without details in 13 trials (graded 'B').

Allocation concealment
Allocation was concealed in 16 trials (graded 'A') and was not reported on in the remaining 6 (graded 'B').

Inclusion of all randomized participants
In 16 trials losses to follow up were less than 10%, and in 6 trials they were not reported but likely

to be below 10%.

Blinding
Four trials blinded the investigator and the trial participants to impregnation, and they did this by using dummy preparations for dipping the nets.

Results

Child mortality from all causes

Five cluster randomized controlled trials examined child mortality from all causes (Table 03). They were all conducted in areas with stable malaria in sub-Saharan Africa: (Burkina (Habluetzel); Gambia (D'Alessand); Ghana (Binka); Kenya (Nevill); Kenya (Phillips-How)). Four of the trials did not use any nets as the control group, and one trial used untreated nets. Both the relative and the absolute impact were analysed.

Relative rate
When the five trials were pooled regardless of the type of control group, the summary relative rate was 0.82 (95% CI: 0.76 to 0.89; Graph 01-01), giving a summary protective efficacy of 18%. The chi^2 test for heterogeneity was not statistically significant ($chi^2 = 1.53$, degrees of freedom = 4, P = 0.82).

Protective efficacy
A regression analysis of the protective efficacy (ln) on the transmission intensity (as measured by the entomological inoculation rate: 10 Gambia (D'Alessand), 30 Kenya (Nevill), 300 Ghana (Binka), 300 Kenya (Phillips-How), 500 Burkina (Habluetzel)) was statistically significant at the 5% level ($r^2 = 0.88$, F = 22.1 on 1,3 degrees of freedom, P = 0.05). The protective efficacy appeared to be lower in areas with a higher entomological inoculation rate, consistent with the hypothesis that relative impact is lower in areas with higher entomological inoculation rates.

Rate difference
It was possible to summarize the rate difference because the trials used similar methods and a similar denominator for their rate calculations (person-years at risk). Each trial corrected the confidence limits in their analysis to take into account cluster allocation (***see*** Table 03). Four trials showed a statistically significant effect, and the direction of effect in the fifth trial favoured treated nets.

The summary rate difference, which expresses how many lives can be saved for every 1000 children protected, was 5.53 deaths averted per 1000 children protected per year (95% CI 3.39 to 7.67; Graph 01-02). I performed a regression analysis of the natural logarithm of the rate difference on the entomological inoculation rate and could not find a trend ($r^2 = 0.52$, F = 3.2 on 1,3 degrees of freedom, P = 0.2). In contrast to protective efficacies, the risk differences seemed to have a tendency towards a higher effect with a higher entomological inoculation rate. This apparent paradox is because the baseline mortality rates are higher in areas with high entomological inoculation rates.

Stratified by type of control group
There was a small non-statistically significant difference in the summary results of protective efficacy in the two comparisons – controls with no nets versus controls with untreated nets: 17% versus 23% reduction in mortality. The summary rate differences in the two comparison groups were virtually identical (5.5 versus 5.6 averted deaths per 1000 per year).

Controls without nets (4 trials)
The summary rate ratio was 0.83 (95% CI 0.76 to 0.90; Graph 01-01), or a protective efficacy of 17%. In other words, overall mortality was reduced by 17% among children aged 1 to 59 months. The chi^2 test for heterogeneity was not statistically significant ($chi^2 = 1.14$, degrees of freedom = 3, P = 0.77).

The risk difference was 5.52 per 1000 protected children per year (95% CI 3.16 to 7.88; Graph 01-02).

Controls with untreated nets (1 trial)
The summary rate ratio was 0.77 (95% CI 0.63 to 0.95; Graph 01-01), or a protective efficacy of 23%. The risk difference was 5.60 deaths per 1000 protected children per year (95% CI 0.50 to 10.70; Graph 01-02).

Malaria-specific child mortality
The impact of ITNs on malaria-specific death rates was looked at only briefly because of the problems using verbal autopsies in determining malaria deaths. In the two trials for which the data were available, the percentage reduction in malaria-specific mortality was similar or smaller than the percentage reduction in all-cause mortality: 14% (versus 23%) for Gambia (D'Alessand), and 22% (versus 18%) for Ghana (Binka). One interpretation is that malaria-specific death rates were not reflecting the true impact of ITNs on mortality (since a much higher specific impact would have been expected).

Severe disease
Only one trial examined severe malarial disease as an outcome Kenya (Nevill). The trial used passive and hospital-based case ascertainment, and observed a 45% (cluster-adjusted 95% CI 20 to 63) reduction in the frequency of severe malaria episodes following the introduction of ITNs (Table 04).

Uncomplicated clinical episodes
The trial results are available in Table 05 for no nets controls and in Table 06 for untreated nets controls. A summary of the main findings for protective efficacies is available in Table 07; confidence intervals were not calculated as this analysis includes both cluster and individually randomized controlled trials. No risk or rate differences were calculated because the denominators were not uniform and the sensitivity of the reporting systems of the different trials is likely to have varied considerably. Three findings can be highlighted.

- The effect of ITNs on uncomplicated clinical episodes of malaria is shown by large effect estimates in all trials. Overall, the reduction in clinical episodes was around 50% for all subgroups (stable and unstable malaria; no nets and untreated nets) and for both *P. falciparum* and *P. vivax*.
- The protective efficacy is higher (at least 11% for *P. falciparum*) when the control group had no nets. This was expected and it was the reason to create two separate comparisons. In areas with stable malaria (entomological inoculation rate > 1) the differences in protective efficacies against uncomplicated malaria was 11% (50% no nets versus 39% untreated nets). In areas with unstable malaria (entomological inoculation rate < 1), the differences were bigger: 23% (62% no nets versus 39% untreated nets) for *P. falciparum*, and 41% (52% no nets versus 11% untreated nets) for *P. vivax*.
- In areas of unstable malaria (entomological inoculation rate < 1), the impact against *P. falciparum* episodes seemed to be higher than the impact against *P. vivax* episodes.

Parasite prevalence
The results are available in Table 08 for no nets and in Table 09 for untreated nets controls. The results for both groups are summarized in Table 10; confidence intervals were not calculated as this analysis includes both cluster and individually randomized controlled trials. Two points can be highlighted from these results.

- In areas of stable malaria, impact on prevalence of infection (measured through cross-sectional surveys) was small: 13% reduction when the control group did not have any nets and 10% reduction when the control group had untreated nets.
- In areas with unstable malaria, the results are of limited value because there was only a single trial in each subgroup (treated versus no nets; and treated versus untreated nets).

High parasitaemia
The results are shown in Table 11 for no nets and Table 12 for untreated nets controls. This outcome was only assessed for trials in areas of stable malaria, where parasitaemia does not necessarily lead to a clinical episode, and where parasitaemia cut-offs are useful to define disease episodes. Five trials measured this outcome: four used 5000 trophozoites/ml as the cut-off, while the fifth trial used an age-specific cut-off (Kenya (Phillips-How)). The protective efficacy was 29% for the two trials in which the control group did not have nets, and was 20% for the three trials in which controls had untreated nets.

Anaemia
The nine trials that measured anaemia were conducted in areas of stable malaria; six trials compared treated to untreated nets (Table 13), and three trials compared treated nets to untreated nets (Table 14).

Overall, the packed cell volume of children in the ITN group was higher by 1.7 absolute packed cell volume per cent compared to children not using nets. When the control group used untreated nets, the difference was 0.4 absolute packed cell volume per cent.

Splenomegaly
Prevalence of splenomegaly was defined as the prevalence rate of children with at least a degree '1' of spleen enlargement on the Hackett's scale. Together with overall mortality it was the only outcome to be properly standardized between the sites (although inter-observer variability can be substantial).

Four out of the five trials that measured splenomegaly were carried out in areas with stable malaria (Table 15 and Table 16). Because the exception was one trial carried out in Thailand whose weight is very small (only 2.6% in the relevant comparison) (Thailand (Luxemburg)), I did not carry out a subgroup analysis.

Splenomegaly was significantly reduced for both types of controls: there is a 30% protective efficacy when controls were not using nets, and a 23% protective efficacy when the control group used untreated nets.

Anthropometric measures
Three trials carried out with ITNs have demonstrated a positive impact on anthropological measurements in children sleeping under treated nets.

In The Gambia (Gambia (D'Alessand)), mean z-scores of weight-for-age and weight-for-height were higher in children from treated villages (-1.36 and -0.98, respectively) than in those from untreated villages (-1.46 and -1.13, respectively). The differences were statistically significant after adjustment for area, age, differential bed net use, and gender (P = 0.008 and P = 0.001, respectively). There was no statistically significant difference in mean z-scores for height-for-age.

In the trial carried out in Kenya (Kenya (Nevill)), infants sleeping under ITNs in the intervention areas had statistically significantly higher z-scores for weight-for-age than control infants not under treated nets (analysis of variance allowing for season, gender, and age: F = 21.63, P = 0.03). Mean mid-upper arm circumference z-scores were also statistically significantly higher among infants in the intervention communities (analysis of variance allowing for survey, gender, and age: F = 19.0, P = 0.005) (Snow 1997).

In Kenya (Kenya (Phillips-How)), protected children under two years of age had a statistically significantly better weight-for-age z-score than unprotected children (P < 0.04). No other statistically significant differences were measured for other parameters or other age groups, although all z-score differences between intervention and control groups were in favour of the protected group.

Discussion

A large number of trials with insecticide-treated bed nets or curtains has been carried out all over the world. We identified 81 trials investigating insecticide-treated mosquito nets or curtains. The 22 trials meeting this review's inclusion criteria span 17 countries. Five of these trials measured mortality, and they showed that the use of ITNs reduces under five mortality in malaria-endemic areas in sub-Saharan Africa by about a fifth.

More trials examined morbidity, and showed an impact of ITNs nets on illness, and on both *P. falciparum* and *P. vivax* infections.

The impact on overall mortality

The relative decrease in mortality (as given by the protective efficacy) afforded by ITNs seemed to be lower in areas with high malaria transmission (entomological inoculation rate > 100) than in areas with a lower transmission rate. However, this was not reflected in terms of absolute risk reduction: the estimated numbers of lives saved per 1000 protected children were similar in all the areas (5.5 lives saved per 1000 children protected per year). With a high coverage of treated nets over two-year period, the benefit of ITNs in terms of lives saved per unit of investment was high in the five trial areas in which overall mortality was measured as outcome.

An approximate extrapolation to the current population of children under five years of age at risk for malaria in sub-Saharan Africa (14% of approximately 480 million population at risk, or 67 million children) indicates that approximately 370,000 child deaths could be avoided if every child could be protected by an ITN.

A cost-effectiveness assessment has shown that ITN programmes compare well in terms of cost-effectiveness with other child survival interventions such as the Expanded Programme on Immunization (EPI) (Goodman 1999).

The impact on morbidity

The impact of ITNs on uncomplicated episodes of malaria is also marked with a halving of episodes under most transmission conditions (stable and unstable malaria). If these results are sustained in large-scale implementation, then ITN programmes could lead to substantial savings both at the healthcare level and at the household level, where the cost of disease episodes is considerable (Sauerborn 1995).

The one trial that demonstrated a substantial impact on severe malaria disease provided evidence that ITNs can have an impact on preventing severe illness and the associated high costs to both patients and healthcare providers (Kenya (Nevill)).

The finding that ITNs improve the haemoglobin level in African children by 1.7% packed cell volume also has important public health implications.

ITNs have a benefit on growth in children too, although these effects appear to be modest.

ITN impact in trials versus programmes
The results presented in this review are from randomized controlled trials where the intervention was deployed under highly controlled conditions, leading to high coverage and use rates. The one exception is Gambia (D'Alessand), which was a randomized evaluation of a national ITN programme in which the intervention deployment was not as good as in the other trials. Therefore, the bulk of data in this review describe impact under ideal trial conditions (efficacy) rather than impact under large-scale programme conditions (effectiveness). While the difference between efficacy and effectiveness is likely to be small for certain medical interventions (such as vaccination or surgery), it can potentially be large for preventive interventions such as ITNs.

Some of the consequences of moving from a scientific trial towards a large-scale programme is illustrated by the results of the two mortality trials carried out in The Gambia. The first trial was carried out under well-controlled implementation conditions, with a high coverage rate in the target population (Gambia (Alonso)). Unfortunately it was not randomized and hence not included in the present analysis. The second one was the evaluation of a national impregnation programme carried out by primary health care personnel and which faced some operational problems (leading, for example, to a lower than expected insecticide dosage) and a lower coverage rate (around 60%) of the target population (Gambia (D'Alessand)). The difference of impact between the two studies is important: the first trial achieved a total reduction in mortality of 42%, while the protective efficacy in the second trial was 23%. It is not clear whether the difference in the baseline mortality rate (42.1 versus 24.3 deaths per 1000 in the control group) played a role in this difference of impact.

Unfortunately, randomization is unlikely to be a feasible option for evaluating most programmes. Impact assessment methodology is not optimal and research is still needed in this area (Lengeler 1996b). Recently, a number of evaluations of small-scale and large-scale programmes have documented good impact on different health parameters (Abdulla 2001; D'Alessandro 1997b; McClean 2002; Rowland 1997; Schellenberg 2001). Most notably, the evaluation of a large social marketing programme in Tanzania showed a 27% improvement in survival in ITN users compared to non-users (Schellenberg 2001) and a substantial (63%) impact on anaemia in children (Abdulla 2001).

A related aspect of programme monitoring is the question of how impact varies with the coverage rate. Especially under high transmission conditions, maximum impact might well be obtained only if a certain level of coverage is achieved and if a substantial part of the mosquito population is killed as a result. Such a "mass effect" has been detected in some trials and not in others, but it is likely that if it is present the impact of ITNs will be enhanced (Lines 1992). Recently, a series of studies have clearly documented a "mass effect" on malaria morbidity (Howard 2000) and especially on child mortality (Binka 1998; Hawley 2003). In Ghana and western Kenya, children living in control areas but within a few hundred meters of an intervention cluster experienced the same reductions in mortality as children in the intervention areas. Since such a "mass effect" is very likely to occur before 100% coverage is achieved, this has potentially important consequences for equity: poorer segments of the population unable to afford an ITN might well benefit from the ITNs used by their better-off neighbours.

Short-term versus long-term benefits
The results from the large-scale ITN trials have re-activated a discussion that has been central in malaria control since the 1950s: does reducing exposure to malaria in areas of very high transmission intensity lead to a long-term gain in mortality or merely to a delay in the time of death? For this review, the relevant question is whether the short-term benefits of ITNs, as seen in trials lasting one to two years, will result in a long-term survival benefit of the protected children.

Different researchers have hypothesized that where malaria transmission is particularly high, the benefits of ITNs will be transitory, and that morbidity and mortality may only be postponed to an older age as a result of preventing the natural development of immunity to malaria that occurs through repeated exposure (Lines 1992; Snow 1994; Snow 1995; Snow 1997; Trape 1996). This does have obvious serious implications for decision-making, and this view has been discussed and sometimes challenged by a number of other authors (D'Alessandro 1997a; Greenwood 1997; Lengeler 1995; Lengeler 1997b; Lines 1997; Molineaux 1997; Shiff 1997; Smith 2001). Despite ongoing disagreements on this question among researchers, there is at least one point on which there is consensus: if such a delay in mortality exists it will only occur in very high transmission areas (a commonly quoted cut-off entomological inoculation rate is 100, although this is at present based on little evidence).

Unfortunately, there is little evidence for or against such a delayed mortality effect following interventions that potentially interfere with the development of natural immunity. The best information comes from two five-year follow-up studies of large ITN trials in Burkina Faso (Diallo 2004) and Ghana (Binka 2002). In both trials the overall survival of children who had slept since birth under an ITN was significantly better than for children who had only received ITNs at the end of the trial. The major implication of these findings is that such a "delayed mortality effect" does not seem to exist, but more studies are needed before this can be proven beyond doubt.

Certainly, stopping or delaying ITN programme implementation because of this fear is not warranted and should even be considered unethical in the light of good evidence of benefit. However, it is important that ITN programmes carried out in areas of high transmission have a well-designed mortality monitoring component alongside implementation.

Comparisons of insecticide-treated nets and indoor residual spraying for malaria control
A number of studies in recent years have compared the implementation of ITNs with the application of indoor residual spraying, the other large-scale vector control intervention. While there have been some arguments about which method is the most efficacious, effective, and cost-effective, the views vary, and some people consider that they are equivalent (Lengeler 2003).

Operational issues
People in malaria endemic areas primarily use bed nets and curtains as a protection against nuisance biting, rather than as a malaria control measure (Zimicki 1996). Since most malarious areas also have a perceived mosquito nuisance problem, treated nets have proved very popular and

large-scale trials had few problems in achieving rapidly high coverage rates and maintain high usage rates for up to three years. Unfortunately, re-treatment of existing nets has proved a much bigger challenge. It is expected that the development of nets with a long-lasting insecticide treatment will offer a solution to this problem.

With the inclusion of ITNs as one of the main strategies for preventing malaria by the Roll Back Malaria partnership, large-scale programmes have started to be implemented in a number of countries. Recently, Roll Back Malaria has developed a global strategy for the up scaling of ITN programmes (RBM 2002), which included a focus on developing of a commercial market for ITNs, as well as additional mechanisms to protect those at highest risk, essentially children and pregnant women. One book chapter has dealt with some of the key operational issues to consider (Feilden 1996), and at least two manuals aimed at national and district level personnel involved in malaria control have been produced (Chavasse 1999; RBM 2003).

Methodological issues

The high proportion of trials that could not be included in the primary review (59 out of the 81 identified trials) is a cause for concern. The main reasons for exclusion were because the studies were not randomized, were not adequately controlled (before and after assessments), and used materials other than bed nets or curtains (such as wall curtains or blankets).

Randomization is important in any intervention study to avoid the investigator's preferences from biasing the results. However, randomization is not always possible, especially if the intervention is considered to be very beneficial. An alternative design can then be required by the ethical review committee, as was the case for the first Gambian trial (Gambia (Alonso)).

Equally important is the fact that potential investigators wanting to test preventive measures that are applied at a group level (for example, at the village level) choose a sufficient number of units to make comparisons meaningful. It is clear that a 1:1 design (one intervention village versus one control village) should not be done because it is highly likely that the two groups will not be comparable at baseline. An absolute minimum of randomization units is six (that is, 3:3), but 10 units would be much better.

Finally, some of the cluster randomized controlled trials presented confidence intervals as if allocation had been on an individual level, described by Cornfield as "an exercise in self-deception" (Cornfield 1978). Trialists, statisticians, and journal editors need to get together to address this widespread problem in trial analysis and publication; and statisticians working in meta-analysis could also help to tackle this problem.

Reviewers' conclusions

Implications for practice

Five randomized controlled trials have provided strong evidence that the widespread use of ITNs can reduce overall mortality by about a fifth in Africa. For every 1000 children protected, on average about 5.5 lives can be saved in children aged 1 to 59 months every year. In Africa, full ITN coverage could prevent 370,000 child deaths per year.

The impact of ITN use on clinical episodes of uncomplicated malaria is also considerable, halving clinical attacks in areas of stable malaria transmission in Africa. One trial in Kenya further documented a substantial impact of ITN use on cases of severe malaria disease seen in hospital. In Asia and Latin America (areas with low malaria transmission, entomological inoculation rate < 1), the use of ITNs also significantly reduced the number of clinical episodes due to both *P. falciparum* and *P. vivax*.

Given the strength of this evidence there is a need to promote the large-scale application of this control tool in the frame of malaria control programmes in endemic areas. The Roll Back Malaria partnership and major international health donors have endorsed this view (WHO 2003).

Because of the lack of data on the long-term impact of ITNs in areas with very high malaria transmission (entomological inoculation rate > 100), a careful monitoring of impact on child survival should be conducted in at least a few sites to provide more data. This consideration is currently not a reason to halt the implementation of ITN programmes.

Implications for research

The beneficial impact of ITNs has been largely demonstrated under trial conditions. Given the consistency of the impact results for different outcomes and different areas of the world, it is unlikely that many more trial data are required. However, four major issues regarding impact assessment remain.

- Firstly, the impact of ITNs under large-scale programme conditions (effectiveness) needs to be better documented for a number of sites and implementation approaches.
- Secondly, a related aspect would be to investigate further how impact varies with ITN coverage rate, and how effectiveness depends on a mass killing of the mosquito population ("mass effect").
- Thirdly, the development of nets with a long-lasting insecticidal activity should be energetically pursued.
- Fourthly, the complex and controversial issue of the long-term impact of reducing malaria transmission in areas of high risk needs to be further explored with clinical, epidemiological, entomological, immunological, and molecular approaches.

In relation to trial reports, researchers and editors need to ensure confidence limits are correctly calculated for cluster randomized controlled trials and that adjusted standard errors are always reported; and meta-analysis specialists could usefully examine how data from cluster randomized controlled trials can be combined.

Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Burkina (Habluetzel)	Study design: cluster randomized controlled trial. Unit of allocation: groups of villages (8 pairs of "clusters" (on average 10 villages) formed on the basis of baseline mortality and geographic similarity). Number of units: 8:8. Length of follow up: 24 months. Mortality was monitored by village reporters and yearly census. A cross-sectional morbidity survey was conducted once, at the peak of the transmission season in September 1995 (n = 800 in 84 villages). All surveys were community-based.	Number of participants: 16,540.Inclusion criteria: children aged 0 to 59 months living in the area (newborns were excluded from the analysis). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated curtains on windows, door, and eaves; target dose of 1000 mg/m2; every house used for sleeping in the intervention clusters fitted with the curtains and re-treated every 6 months. Control: no curtains.	(1) Overall mortality (1 to 59 months). (2) Prevalence of parasitaemia (any). (3) Prevalence of high parasitaemia (> 5000 trophozoites per ul). (4) Anaemia (mean haemoglobin in g/dl).	Study location: Oubritenga Province, 30 km north of Ouagadougou, in a rural area. EIR: 300 to 500. Malaria endemicity: holoendemic. Baseline parasite rate in children 6 to 59 months: 85%. Main vectors: Anopheles gambiae s.l. and A. funestus. Plasmodium vivax malaria: 0%. Dropout rate unknown, but immigration/emigration rates were low (2% per year). Access to health care considered poor.	A
Cameroon (Moyou-S)	Study design: individual randomized controlled trial. Unit of allocation: household (20 households were chosen in each "quartier" (methods not stated)). Number of units: 20:20. Length of follow up: 12 months. Monitoring from January to	Number of (randomized) participants: approximately 480 children aged 0 to 15 years from 20 households. Inclusion criteria: people living in 2 neighbourhoods.	Intervention: deltamethrin-treated bed nets; target dose 25 mg/m2; nets treated in January 1992 and re-treated in August 1992. Control: no bed nets; < 20% usage.	(1) Prevalence of any parasitaemia (repeated measure). (2) Splenomegaly (Hackett 1 to 5).	Study location: Kumba (South-West Province), Cameroon. EIR: 10 to 20. Malaria endemicity: hyperendemic. Baseline parasite rate in children aged 0 to 15 years: 30.2 to 52.5%. Main vector: Anopheles	B

	December 1992. Overall survey completion rate 75%. Repeated cross-sectional surveys carried out in February, April, June, August, October, and December 1992 (on average, n = 361, 75.2% of the group).				gambiae s.l. Plasmodium vivax malaria: 0%. Access to health care was likely to be good.	
Colombia (Kroeger)	Study design: cluster randomized controlled trial. Unit of allocation: village (22 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; within each pair 1 village within each pair was then randomized to receive the intervention). Number of units: 11:11. Length of follow up: 12 months. Single cross-sectional survey carried out during the peak of the malaria season in February to March 1992.	Number of participants: 4632 participants took part in the cross-sectional survey (high percentage of total). Inclusion criteria: inhabitants of the 22 trial communities.	Intervention: lambdacyhalothrin treatment of existing bed nets; target dose 10 to 30 mg/m2; net treatment in September and November 1991 (nearly 60% of all existing nets were treated at least once); sales and promotion of bed nets, and free net treatment. Control: untreated bed nets; 96% usage rate).	(1) Period-prevalence (last two weeks or last four months) of reported "malaria episodes" assessed during the peak of the malaria season (March to April 1992). Outcome measures similar to Ecuador (Kroeger).	Study location: lower Rio San Juan, Departamente Choco on the Pacific Coast, Colombia. EIR: < 1. Malaria endemicity: hypoendemic. Baseline parasite rate in the whole population and spleen rate in children aged 2 to 9 years: below 5%. Main vector: Anopheles nevai. Plasmodium vivax malaria: 31% of all episodes; no distinction made between P. falciparum and P. vivax in the analysis. Usage rate was high (96% of families with at least one net). Access to health care was likely to be good.	B
Ecuador (Kroeger)	Study design: cluster randomized controlled trial. Unit of allocation: village (14	Number of participants: 2450 participants took part in the cross-sectional survey (high	Intervention: permethrin treatment of existing bed nets; target dose 200 mg/m2;	(1) Period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes"	Study location: Canton Muisne, on the northern Coast, Ecuador.	B

	villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair then randomized to receive the intervention). Number of units: 7:7. Length of follow up: 17 months. Single cross-sectional survey carried out during the peak of the malaria season in March to April 1992.	percentage of total). Inclusion criteria: inhabitants of the 14 trial communities.	high usage rate high (93% of families with at least 1 net); net treatment in October and December 1991 (6 and 4 months before the evaluation); nearly 80% of all existing nets were treated at least once; sales and promotion of bed nets, and free net treatment. Control: untreated bed nets; > 90% usage rate.	assessed during the peak of the malaria season (March to April 1992). Although no systematic parasitological confirmation was done, quality control procedures ensured adequate accuracy. According to a pilot phase, about 88% to 96% of the self-diagnoses were based on the same criteria as health professionals. In addition, time trends were compared to those obtained from routine data.	EIR: < 1. Malaria endemicity: hypoendemic. Baseline parasite rate in the whole population and spleen rate in children aged 2 to 9 years: < 5%. Main vector: Anopheles albimanus. Plasmodium vivax malaria: 51% of all episodes; no distinction could be made between episodes due to P. falciparum or P. vivax in the analysis. Access to health care was likely to be good.	
Gambia (D'Alessand)	Study design: cluster randomized controlled trial. Unit of allocation: village (52 pairs of villages formed on the basis of size, after stratification by 5 geographical areas). Number of units: 58:52. Length of follow up: 12 months. Dropout rate unknown, but immigration/emigration rates were low (< 5% per year). Mortality monitored by village reporters and yearly census. Morbidity surveys	Inclusion criteria: children aged 0 to 9 years and living in the area were eligible at the start, but later the analysis was restricted to children aged 1 to 59 months (n = 25,000). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: treatment of existing bed nets in the frame of a national programme; target dose 200 mg/m2 permethrin; impregnation done by village health workers with the assistance of other community members and under the supervision of community health nurses; re-treatment was not done during the 1 year follow-up period since the transmission season lasts only about 4 months. Control: untreated bed nets.	(1) Overall mortality (1 to 59 months). (2) Prevalence of parasitaemia (any). (3) Prevalence of high parasitaemia (> 5000 trophozoites per ul). (4) Anaemia (mean packed cell volume). (5) Prevalence of splenomegaly (1 to 5 Hackett). (6) Impact on nutritional status (weight-for-age, weight-for-height).	Study location: 5 distinct areas spread over the whole of The Gambia (all rural areas). EIR: 1 to 10. Malaria endemicity: hyperendemic. Baseline parasite rate in children 12 to 59 months: 39%. Main vector: Anopheles gambiae s.l. Plasmodium vivax malaria: very low; not taken into account for analysis. Access to health care moderately easy.	A

	were conducted once, at the peak of the transmission season in October (n = 1500 in 50 villages). All surveys were community-based.		Usage rate around 70% in both intervention and control areas (varied between 50% and 90% according to the area).			
Gambia (Snow I)	Study design: individual randomized controlled trial. Unit of allocation: household (allocation of 110 compounds was done randomly after stratification by 3 levels of "spleen rate": no child with enlarged spleen in household, one child, more than one child). Number of units: 60:50. Length of follow up: 4 months. Morbidity rates monitored longitudinally by weekly home visits during 4 months in the peak transmission season (July 1985 to November 1985). A blood slide was made if the child had an axillary temperature of at least 37.5 °C, or if the mother reported that the child had had fever during the last 3 days. Success rate for weekly visits was 97%. Overall dropout rates were	Number of eligible participants: 580. Number of randomized participants: 389 (67%). Inclusion criteria: children aged 1 to 9 years living in the village. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin treatment of existing bed nets; target dose 500 mg/m2; usage rate was very high before the trial (98%); nets not re-treated because of the short duration of the trial. Control: dilute crystal violet solution (placebo treatment) used to treat control nets; 98% usage rate.	(1) Incidence of mild clinical episodes (children aged 1 to 9 years). (2) Prevalence of any parasitaemia. (3) Prevalence of high parasitaemia (> 5000 parasites/ul). (4) Prevalence of anaemia (mean packed cell volume).	Study location: village of Katchang, on the north bank of the Gambia River, Gambia. EIR: 10. Malaria endemicity: hyperendemic. Baseline parasite rate in children 1 to 9 years: 8.6% in the low season and 43.1% in the peak season. Main vector: Anopheles gambiae s.l. Plasmodium vivax malaria: 0%. Access to health care was considered poor.	A

	8% in the treatment group and 12% in the control group. Single cross-sectional morbidity survey conducted at the end of the transmission season in November 1985 (n = 275). All surveys were community-based.					
Gambia (Snow II)	Study design: cluster randomized controlled trial. Unit of allocation: village (allocation of 16 villages was done randomly after stratification by previous net provision and location with regard to a river). Number of units: 7:9. Length of follow up: 4 months. Morbidity rates monitored longitudinally by weekly home visits during 4 months in the peak transmission season (July 1987 to November 1987). Blood slide made if the child had an axillary temperature of at least 37.5 C. Mothers also asked about the well-being of their child on the day of the interview. Completion rate for weekly visits was 95%. Overall dropout rates were	Number of eligible participants: 491. Number of randomized participants: 454 (92%). Inclusion criteria: children aged 1 to 9 years living in the village. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin treatment of existing bed nets; target dose 500 mg/m2; usage rate was very high before the trial (> 95%); nets not re-treated because of the short duration of the trial. Control: dilute milk in water solution (placebo treatment) used to treat control nets; > 95% usage rate.	(1) Incidence of mild clinical episodes (children aged 1 to 9 years). (2) Prevalence of any parasitaemia. (3) Prevalence of high parasitaemia (> 5000 parasite/ul). (4) Prevalence of anaemia (mean packed cell volume). (5) Prevalence of splenomegaly (Hackett 1 to 5).	Study location: 16 Fula villages, on the north bank of the Gambia River, west of Farafenni, Gambia. EIR: 10. Malaria endemicity: hyperendemic. Baseline parasite rate in children 1 to 9 years: 25.9% in the low season and 37.3% in the peak season. Main vector: Anopheles gambiae s.l. Plasmodium vivax malaria: 0%. Access to health care was considered poor.	A

	11% in both treatment groups. Single cross-sectional morbidity survey was conducted at the end of the transmission season in November 1985 (n = 422). All surveys were community-based.					
Ghana (Binka)	Study design: cluster randomized controlled trial. Unit of allocation: village (allocation of 96 "clusters" was done randomly (public ballot) after stratification by 10 chiefdoms). Number of units: 48:48. Length of follow up: 24 months (July 1993 to June 1995). Dropout rate unknown, but immigration/emigration rates were low (< 5% per year). Mortality was monitored by village reporters and 4-monthly censuses (rolling census). A cross-sectional morbidity survey was conducted twice, in June 1994 (n = 2799) and at the peak of the transmission season in October 1994 (n = 3788). All surveys were	Number of participants: 19,900. Inclusion criteria: children aged 0 to 59 months living in the area (newborns were excluded from the analysis). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated bed nets; target dose 500 mg/m2; enough bed nets distributed to protect both children and the adults; nets re-treated every 6 months. Control: no bed nets; 4% usage (very low). No co-intervention at the time of the trial.	(1) Overall mortality (1 to 59 months). (2) Prevalence of parasitaemia (any). (3) Prevalence of high parasitaemia (> 4000 trophozoites per ul). (4) Anaemia (mean haemoglobin in g/dl).	Study location: rural area in the Kassena-Namkana, in the Upper East Region of Ghana. EIR: 100 to 300. Malaria endemicity: holoendemic. Baseline parasite rate in children 6 to 59 months: 85 to 94% in the peak season, with strong seasonal fluctuation. Main vectors: Anopheles gambiae s.l. and A. funestus. Plasmodium vivax malaria: < 2% (not taken into account in the analysis). Access to health care poor.	A

	community-based.					
Iran (Zaim I)	Study design: cluster randomized controlled trial. Unit of allocation: village (random allocation of 13 villages (10 intervention, 3 control) from a list of eco-epidemiologically homogenous villages). Number of units: 10:3. Length of follow up: 8 months. Morbidity rates monitored longitudinally by passive case detection (high access to health care) as well as home visits every 10 days. Monitoring from April to November 1995, covering the 2 peaks in transmission (April to May and September to October). Blood slide was made for every person reporting with symptoms compatible with malaria; every positive slide labelled a "malaria case" and no differentiation between Plasmodium falciparum and P. vivax malaria made in the analysis. All surveys were community-based.	Number of participants: 6507. Inclusion criteria: persons living in the village. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: cyfluthrin treatment of existing cotton bed nets through health workers supervised by the researchers; target dose 40 mg/m2; usage rate very high before the trial (nearly every family reported to have at least 1 net). Control: untreated bed nets; usage rate not specified but very high. Co-intervention: residual spraying with propoxur (2 g/m2) stopped 7 months before start of the trial. As a result, mosquito population unlikely to be "natural" at the start of the trial.	(1) Incidence of mild clinical episodes (all ages).	Study location: 13 villages in Ghasseregahnd (Baluchistan) in Iran. EIR: very low. Malaria transmission: unstable, with 30 to 50 infections per 1000 inhabitants per year. Main vectors: Anopheles culicifacies and A. pulcherrimus. Plasmodium vivax malaria: 25% to 63% (mean = 53%) of all cases.	A
Ivory Coast (Henry)	Study design: cluster	Number of participants: 432.	Intervention:	(1) Prevalence of	Study location: 8 villages	B

	randomized controlled trial. Unit of allocation: village (allocation of 8 villages by paired randomization). Number of units: 4:4 Length of follow up: 12 months. Evaluation by cross-sectional surveys and by active case surveillance.	Inclusion criteria: children aged 0 to 59 months.	lambdacyhalothrin-treated nets; target dose 15 mg/m2; high usage rate; n = 216. Control: no nets; n = 216.	parasitaemia, anaemia and incidence of clinical episodes. (2) Anaemia. (3) Incidence of clinical episodes.	around the town of Korhogo, in northern Ivory Coast. EIR: 55. Baseline prevalence rate in small children: 69%. Plasmodium vivax malaria: no information available.	
Kenya (Nevill)	Study design: cluster randomized controlled trial. Unit of allocation: village (random allocation of 56 "clusters" (of ~1000 participants each) after stratification by 3 geographical areas). Number of units: 28:28. Length of follow up: 24 months (July 1993 to June 1995). Dropout rate unknown, but immigration/ emigration rates were low for young children. Mortality monitored by village reporters and 6-monthly censuses. Cross-sectional morbidity surveys were conducted in	Number of participants: 11,000. Inclusion criteria: children aged 0 to 4 years living in the area (newborns were excluded from the analysis). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated bed nets; target dose 500 mg/m2; enough distributed to protect all children; nets re-treated every 6 months. Control: no bed nets; 6% usage (very low).	(1) Overall mortality (1 to 59 months). (2) Incidence of admission with severe malaria disease at the district hospital (1 to 59 months). Case definition: children with Plasmodium falciparum parasitaemia and no other obvious cause of disease; for cerebral malaria: coma or prostration or multiple seizures; severe malaria anaemia was defined as < 5.1 g/dl haemoglobin with more than 10,000 parasites per ul. (3) Prevalence of parasitaemia in infants aged 9 to 12 months (any). (4) Impact on anthropometric parameters (weight-for-age and mid-upper arm circumference).	Study location: in a rural area in Kilifi District on the Kenyan Coast. EIR: 10 to 30. Malaria endemicity: hyperendemic. Baseline parasite rate in children 1 to 9 years: 49% in the peak season, with seasonal fluctuation. Main vector: Anopheles gambiae s.l. Plasmodium vivax malaria: 0%. Access to health care is good and over 10% of all children under 5 years are admitted per year.	A

	infants only (1 to 12 months) after peak of the transmission season in August 1994 (n = 443), January 1995 (n = 540), and March 1995 (n = 496). Monitoring system also was set up at Kilifi District hospital to register all admissions with severe malaria disease. All surveys were community-based.					
Kenya (Phillips-How)	Study design: cluster randomized controlled trial. Unit of allocation: village (allocation of 221 villages by open lottery). Number of units: 113:108. Length of follow up: 24 months. Mortality was monitored by a full demographic system, a birth cohort study, and cross-sectional surveys.	Number of participants: 18,500. Inclusion criteria: children aged 0 to 59 months; (newborns were excluded from the analysis).	Intervention: permethrin-treated polyester bed nets; target dose 500 mg/m2; usage rate very high 66% during last night. Control: no nets.	(1) Overall mortality. (2) Clinical incidence. (3) Parasite prevalence. (4) Anaemia. (5) Anthropometric measurements.	Study location: Asembo and Gem areas of Siaya District, western Kenya. EIR: 60 to 300 (high). Plasmodium falciparum parasite rate in young children: 88%. Plasmodium vivax malaria: no information available.	A
Kenya (Sexton)	Study design: individual randomized controlled trial. Unit of allocation: household (105 families, each with at least one child < 5 years of age were selected randomly from two villages and then allocated randomly to 1 of 3 groups: treated bed nets, treated curtains, or control).	Number of participants: 477. Inclusion criteria: persons living in the villages (primary analysis was for all ages). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention 1: permethrin-treated bed nets; target dose 500 mg/m2; usage rate very low before the trial (9%); nets not re-treated because of short duration of the trial; n = 154. Intervention 2: permethrin-treated curtains	(1) Incidence of reported fever (all ages). Results for treated bed nets and treated curtains were not significantly different and were therefore pooled ("intervention group").	Study location: 2 villages in western Kenya (52 km from Kisumu). EIR: 300. Malaria endemicity: holoendemic. Baseline parasite rate in children < 5 years: 87.4%, with little seasonal fluctuation.	A

	Number of units: 35:35. Length of follow up: 4 months. Re-infection rates after radical treatment with sulfadoxine-pyrimethamine (Fansidar) monitored longitudinally by weekly home visits during 4 months in the low transmission season (August 1988 to November 1988). Blood slide made at each visit. In addition, clinical episodes (mainly fever and chills) were recorded twice per week. Participants reporting fever or a history of fever since the last visit had their axillary temperature taken. Completion rate for weekly visits was around 60%. Overall dropout rates were 3% in the bed net group and 0% in the 2 other groups. All surveys were community-based.		(eaves, door, windows); target dose 500 mg/m2; usage rate very low before the trial (9%); nets not re-treated because of short duration of the trial; n = 167. Control group: no bed nets, no curtains; maximum 9% usage rate; n = 156.		Main vector: Anopheles gambiae s.l. Plasmodium vivax malaria: 0%. Access to health care was not very good, but there was a high use of antimalarials.	
Madagascar(Rabariso)	Study design: individual randomized controlled trial. Unit of allocation: household (91 households (n = 501)). Number of units: 46:45. Length of follow up: 15	Number of participants: 244 people lived in intervention houses, and 257 in control houses. Inclusion criteria: persons living in 1 town area were	Intervention: deltamethrin-treated curtains (door, windows); target dose 25 mg/m2; nets re-treated before each transmission season.	(1) Incidence of malaria episodes (all ages + children aged 0 to 9 years).	Study location: town of Ankazobe (100 km from Antananarivo, at 1300m altitude) in Madagascar. EIR: 2, very seasonal transmission.	A

	months. Overall dropout rates were 15% in the bed net group and 13% in the control group. Follow up through passive case detection at the Institut Pasteur dispensary set up in the study area. Clinics were held daily and every participant had an axillary temperature taken and a blood slide made. Case of malaria was defined as a temperature of at least 37.5 C and a Plasmodium falciparum parasitaemia of at least 1500 parasites per ul. Monitoring carried out in February to July 1993 and in January to June 1994 (total 12 months) during the high transmission season. All surveys were community-based.	eligible (primary analysis was for all ages). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Control group: untreated curtains. No information available on usage rates.		Malaria endemicity: mesoendemic. Main vector: Anopheles funestus. Plasmodium vivax malaria: 0%. Access to health care was good.	
Nicaragua (Kroeger)	Study design: cluster randomized controlled trial. Unit of allocation: village (20 villages were paired according to size, socioeconomic conditions, and malaria incidence at baseline; 1 village within	Number of participants: 5260 individuals took part in the cross-sectional survey (high percentage of total). Inclusion criteria: inhabitants of the 20 trial communities.	Intervention: lambdacyhalothrin treatment of existing bed nets; target dose 13 mg/m2; 75% usage rate (high); sales and promotion of bed nets, and free net treatment.	(1) Period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season. Outcome measures similar to Ecuador (Kroeger).	Study location: El Viejo Municipio, Department of Chinandega, North East Nicaragua (Pacific coast). EIR: well below 1. Malaria endemicity: hypoendemic. Baseline parasite rate in the	B

	each pair then randomized to receive the intervention). Number of units: 10:10. Length of follow up: 4 months. For the evaluation, 1 cross-sectional survey carried out during the peak of the malaria season in 1996.		Control group: no nets; (< 25% usage rate of untreated nets).		whole population: 8%. Main vector: Anopheles albimanus. Plasmodium vivax malaria: virtually all infections due to P. vivax. Access to health care was likely to be good.	
Pakistan (Rowland)	Study design: individual randomized controlled trial. Unit of allocation: household (random allocation of 192 households with 2792 individuals of all ages after a first random selection of 10% of all households from a census list; the aim of this procedure was to measure the impact of treated nets in a condition of low net usage). Number of units: 173:186. Length of follow up: 6 months. Morbidity rates monitored longitudinally by passive case detection in a project clinic. Blood slide made for all suspected malaria cases; each positive blood slide was a case. Monitoring was from June to December 1991,	Number of participants: 2792 (all ages). Inclusion criteria: chosen from 2 Afghan refugee camps: Baghicha and Kagan. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated polyester bed nets; target dose 500 mg/m2; 2% usage rate before the trial (very low). Control group: no bed nets; < 2% usage rate.	(1) Incidence of mild clinical episodes (all ages) for both Plasmodium falciparum and P. vivax. (2) Prevalence of any parasitaemia (P. falciparum and P. vivax).	Study location: Mardan District, North West Frontier Province, North West Pakistan. EIR: low. Malaria transmission is unstable in the area, with 22% of individuals reporting having had malaria in the past year. Parasite rates: 2.4% for P. falciparum and 10.9% for P. vivax. Main vectors: Anopheles culicifacies and A. stephensi. Plasmodium vivax malaria: 77% of all cases (kept separate in analysis). Good access to health care.	A

	covering the main transmission period. Overall completion rate was 97%. A single cross-sectional survey was carried out in December 1991 to January 1992.					
Peru Amaz (Kroeger)	Study design: cluster randomized controlled trial. Unit of allocation: village (36 communities were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention). Number of units: 18:18. Length of follow up: 17 months. For the evaluation, one cross-sectional survey was carried out in April 1992.	Number of participants: 5709 individuals took part in the cross-sectional survey (high percentage of total). Inclusion criteria: inhabitants of the 36 trial communities.	Intervention: permethrin treatment of existing bed nets; target dose 200 mg/m2; usage rate very high (95% of families with at least one net); net treatment in November 1991 and January 1992; nearly 61% of all existing nets treated at least once; free bed net treatment (sales were not necessary because of the high usage rate). Control group: untreated bed nets; 95% usage rate.	Period-prevalence (last two weeks or last four months) of reported "malaria episodes" assessed in April 1992. Outcome measures similar to Ecuador (Kroeger).	Study location: Tambopata District, Madre de Dios Department in the Amazonas region of Peru. EIR: < 1, little seasonality. Malaria endemicity: hypoendemic. Baseline parasite rate in the whole population and spleen rate in children aged 2 to 9 years: < 5%. Main vectors: Anopheles evansae and A. nunetzovari. Plasmodium vivax malaria: 100%. Access to health care was likely to be good.	B
Peru Coast (Kroeger)	Study design: cluster randomized controlled trial. Unit of allocation: village (12 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention). Number of units: 6:6.	Number of participants: 6941 individuals took part in the 2 cross-sectional surveys (high percentage of total). Inclusion criteria: inhabitants of the 12 trial communities.	Intervention: lambdacyhalothrin (first year; target dose 10 mg/m2) or permethrin (second year; target dose 500 mg/m2) treatment of existing bed nets; moderate usage rate (63% of families with at least 1 net); net treatment in January and March 1992 and 1993; nearly 67% of all	(1) Period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season (June to July 1992/1993). Outcome measures similar to Ecuador (Kroeger).	Study location: Communidad de Catacaos, Piura Department, northern Peru on the Pacific Coast. EIR: < 1. Malaria endemicity: hypoendemic. Baseline parasite rate in the whole population and spleen rate in children aged 2 to 9 years: < 5%.	B

	Length of follow up: 29 months. 2 cross-sectional surveys carried out during the peak of the malaria season in June to July 1992 and 1993.		existing nets treated at least once; sales and promotion of bed nets, and free net treatment. Control group: untreated bed nets; 63% usage rate.		Main vector: Anopheles albimanus. Plasmodium vivax malaria: 100%. Access to health care was likely to be good.	
Sierra Leone (Marb)	Study design: cluster randomized controlled trial. Unit of allocation: village (17 villages were paired according to size, altitude, climate, and presence of a health centre; 1 village in each pair was then randomized to the intervention; children were also randomized individually to either chemoprophylaxis with pyrimethamine/dapsone (Maloprim) or placebo - my analysis focused on the placebo group in order to exclude the effect of chemoprophylaxis). Number of units: 9:9. Length of follow up: 12 months. Overall dropout rates were 17% in the bed net group and 18% in the control group. Follow up through weekly	Number of participants randomized: 920 treated nets (n = 470) or no nets (n = 450). Inclusion criteria: children aged 3 months to 6 years. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: lambdacyhalothrin-treated bed nets; target dose 10 mg/m2. Control group: no bed nets; very low usage rate. In addition, children were randomized individually to either chemoprophylaxis with pyrimethamine/dapsone (Maloprim) or placebo.	(1) Incidence of malaria episodes (children aged 3 months to 6 years). (2) Prevalence of anaemia (mean packed cell volume). (3) Prevalence of splenomegaly (Hackett 1 to 5).	Study location: 17 villages near the town of Bo, Sierra Leone. EIR: 35. Malaria endemicity: hyperendemic. Baseline parasite rate in children aged 1 to 5 years: 49.2%. Main vector: Anopheles gambiae. Plasmodium vivax malaria: 0%. Access to health care was considered poor.	A

	visits to all study children. A short questionnaire was administered to the mother, and the temperature of the child was recorded. Blood slide made if the child was reported to have been ill during the last 7 days or if the temperature was at least 37.5 C; case of malaria recorded if the slide revealed a parasitaemia of at least 2000 parasites per ul (children under 2 years) or at least 5000 parasites per ul (children aged 2 to 6 years). Monitoring from July 1992 to June 1993. A cross-sectional survey was carried out in March 1993. All surveys were community-based.					
Tanzania (Fraser-H)	Study design: individual randomized controlled trial. Unit of allocation: individual (random allocation of 120 children aged 5 to 24 months from an existing village list). Number of units: 120 children. Length of follow up: 6 months.	Number of participants: 120. Inclusion criteria: children aged 5 to 24 months.	Intervention: permethrin-treated polyester bed nets; target dose 500 mg/m2; 90% usage rate (very high). Control group: no nets.	(1) Parasitaemia. (2) Haemoglobin. (3) Multiplicity of infections measured during repeated cross-sectional survey.	Study location: Kiberege village, Kilombero District, Tanzania. EIR: high (around 300 per year). Plasmodium falciparum prevalence rate in this age group: 60%. Main vectors: Anopheles gambiae s.l. and A. funestus,	B

					Plasmodium vivax malaria: no information available.	
Thailand (Kamol-R)	Study design: individual randomized controlled trial. Unit of allocation: household (random allocation of 54 households with 270 adults after stratifying for malaria endemicity). Number of units: 26:28. Length of follow up: 8 months. Morbidity rates monitored longitudinally by weekly follow up at which blood slides were taken systematically; each positive blood slide was a case. Monitoring from November 1987 to July 1988 (35 weeks) covering the main transmission period. Completion rates were 96 and 97%. Differentiation made between Plasmodium falciparum and P. vivax malaria (40% of all cases).	Number of participants: 261. Inclusion criteria: adult migrant workers (male:female ratio was 1.4). Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated nylon bed nets; target dose 500 mg/m2; approximately 87% usage rate before trial. Control group: untreated bed nets; > 95% usage rate.	(1) Incidence of mild clinical episodes (adults) for both P. falciparum and P. vivax.	Study location: Bothong District, Chonburi Province (rural) in eastern Thailand. EIR: low. Malaria transmission is unstable in the area. Main vector: Anopheles dirus. Plasmodium vivax malaria: 43% of all cases (kept separately in analysis). Good access to health care.	B
Thailand (Luxemburg)	Study design: individual randomized controlled trial. Unit of allocation: individual (random allocation of 350 children aged 4 to 15 years from an existing list of all	Number of participants: 318. Inclusion criteria: children aged 4 to 15 years. Exclusion criteria: no explicit exclusion criteria except absence of written consent.	Intervention: permethrin-treated cotton bed nets; target dose 500 mg/m2; approximately 70% usage rate before trial.	(1) Incidence of mild clinical episodes (5 to 14 years) for both P. falciparum and P. vivax. (2) Prevalence of any parasitaemia.	Study location: Shoklo (Karen) refugee camp in northern Thailand. EIR: low. Malaria transmission is unstable in the area, with 800	B

	school children). Number of units: 175:175. Length of follow up: 7 months. Morbidity rates monitored longitudinally by passive case detection (high access to health care) as well as through the identification of school absentees who were brought to the dispensary for examination. Monitoring from August 1990 to February 1991, covering 1 of the 2 peaks in transmission (December to January). Blood slide made for every person reporting with a febrile illness compatible with malaria; every positive slide labelled a "malaria case"; differentiation made between Plasmodium falciparum and P. vivax malaria (30% of all cases). 2 cross-sectional surveys conducted at 3 and 6 months (92% participation rate).		Control group: untreated bed nets; > 95% usage rate. Co-intervention: 22% use of treated nets at baseline.	(3) Prevalence of splenomegaly.	infections/1000 inhabitants/ year in that age group. Main vectors: Anopheles dirus and A. minimus (likely main vectors). Plasmodium vivax malaria: 30% of all cases (kept separate in analysis). Good access to health care.

EIR: entomological inoculation rate (the number of times on average a person living in the area receives an infected mosquito bite); units = bites/person/year.
Quality of allocation concealment: A, adequate, for example, using central randomization; B, unclear, no method reported or the approach was not 'A'; C, inadequate, method is not concealed,

for example, using case record numbers.

Characteristics of excluded studies

Study ID	Reason for exclusion
Afghanistan(Rowland)	Treated chaddar and top sheets, not nets or curtains.
Benin (Akogbeto)	Non-randomized allocation of 2 areas within 1 large village.
Brazil (Santos)	Non-randomized allocation of 60 households in 2 villages.
Burkina (Carnevale)	Non-randomized allocation of 2 areas within 1 village.
Burkina (Pietra)	Non-randomized allocation of 2 areas within 1 village.
Burkina F (Procacci)	Non-randomized allocation of 2 clusters within 1 village.
Cambodia (Chheang)	Non-randomized allocation of 2 “blocks” of each 2 hamlets.
Cameroon (LeGoff)	No contemporaneous control group; before-after assessment.
China (Cheng Hailu)	Non-randomized allocation of 20 villages.
China (Li)	No proper control group but comparison of users and non-users; before-after comparison.
China (Luo Dapeng)	Non-randomized allocation of 5 villages.
China (Wu Neng I)	Non-randomized allocation of 3 townships.
China (Wu Neng II)	Non-randomized allocation of 2 villages.
China (Yuyi station)	Non-randomized allocation of 3 villages.
Ecuador (Yepez)	Non-randomized allocation of 2 villages.
Gambia (Alonso)	Non-randomized allocation of 70 villages
Guatemala (Richards)	Non-randomized allocation of 3 villages; a further 100 households in 2 additional villages allocated randomly to treated bed nets or no bed nets.
Guinea-B. (Jaenson)	Non-randomized controlled trial; and mechanism of allocation not clear.
India (Banerjee)	Military personnel and not general population.
India (Das)	Non-randomized allocation of 3 villages.
India (Jana-Kara)	Non-randomized allocation of 12 villages.

India (Yadav I)	Non-randomized allocation of 6 villages.
India (Yadav II)	Non-randomized allocation of 10 villages.
India (Yadav III)	Non-randomized allocation of 5 villages.
Indonesia (Nalim)	Non-randomized allocation of 4 villages.
Iran (Zaim II)	Non-randomized allocation of 5 villages.
Irian Jaya (Sutanto)	Non-randomized allocation of 2 villages.
Ivory Coast(Doannio)	Non-randomized allocation of 2 areas in 1 large village.
Kenya (Beach)	Non-randomized allocation of 3 villages blocks.
Kenya (Macintyre)	Treatment of bed sheets ("shukas"), not sheets or curtains.
Kenya (Mutinga)	Non-randomized allocation of 3 villages.
Kenya (Oloo I)	Non-randomized allocation of 20 houses.
Kenya (Oloo II)	Non-randomized allocation of 2 villages.
Malawi (Rubardt)	Non-randomized allocation of 12 villages.
Malaysia (Hii I)	Non-randomized allocation of 6 villages.
Malaysia (Hii II)	Non-randomized allocation of 22 villages.
Mali (Doumbo)	Non-randomized allocation of 2 villages.
Mali (Ranque)	Non-randomized allocation of only 10 households.
Mozambique (Crook)	Non-randomized allocation of 2 areas within part of Maputo (the capital city).
Myanmar (Lwin)	Non-randomized allocation of 2 areas within 1 township.
Nepal (Sherchand)	Non-randomized allocation of 5 village development committees.
Nigeria (Brieger)	Non-randomized allocation of 12 village clusters (into 4 treatment arms).
Papua NG (Graves)	Non-randomized allocation of 8 paired villages.
Philippines(Quilala)	Allocation “by chance” of the intervention to 6 villages.
Senegal (Faye)	Non-randomized allocation of 2 villages.
Solomon (Hii)	Non-randomized allocation of 2 zones.
Solomon (Kere I)	Non-randomized allocation of 2 zones.
Solomon (Kere II)	Non-randomized allocation of 3 areas.

Sudan (El Tayeb)	Non-randomized allocation of only 2 villages.
Tanzania (Lyimo)	Non-randomized allocation of only 4 villages.
Tanzania (Maxwell)	Non-randomized allocation of control villages.
Tanzania (Njau)	Non-randomized allocation of 368 households in 1 large village.
Tanzania (Njunwa)	Non-randomized allocation of 4 villages.
Tanzania (Premji)	Non-randomized allocation of 7 villages in 2 blocks.
Tanzania (Stich)	Non-randomized allocation of 2 villages (2 phases, 3 years apart, in a cross-over design).
Vietnam (Dang)	Allocation "by chance" of the intervention to 200 workers:
Vietnam (IMPE)	Non-randomized allocation of 2 villages.
Vietnam (Nguyen)	Non-randomized allocation of 13 hamlets.
Zaire (Karch)	Non-randomized allocation of 3 villages.

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Table of comparisons

Additional tables

01 Search strategies for databases

Search set	CIDG* trial register	CENTRAL	MEDLINE (PubMED)**	EMBASE (OVID)	LILACS
(1)	malaria	malaria	malaria [mesh]	malaria/	malaria
(2)	Plasmodium	Plasmodium	plasmodium/	malaria control/	bednet
(3)	bednet	bednet	1 or 2	malaria falciparum/	insecticide
(4)	mosquito net	mosquito net	bednet/	1 or 2 or 3	curtain
(5)	curtain	curtain	mosquito net/	bednet/	--
(6)	insecticide	insecticide	curtain/	curtain	--
(7)	--	--	4 or 5 or 6	5 or 6	--
(8)	--	--	deltamethr*	deltamethrin/	--
(9)	--	--	cyfluthrin*	cyrluthrin/	--
(10)	--	--	impregnated/	insecticide/	--
(11)	--	--	pyreth*	pyrethroid/	--
(12)	--	--	lambdacyhal*	lambdacyhal/	--
(13)	--	--	insecticide-treated	8 or 9 or 10 or 11 or 12	--
(14)	--	--	8 or 9 or 10 or 11 or 12 or 13	4 and 7 and 13	--
(15)	--	--	3 and 7 and 14	--	--
	*CIDG: Cochrane Infectious Diseases Group		**Search terms used in combination with the search strategy for retrieving trials		

			developed by The Cochrane Collaboration (Alderson 2004)		

Additional tables

02 Randomization and outcomes

Study	Types of controls	Unit of allocation*	Child mortality**	Uncomplic. episodes	Parasite prevalence	High parasitaemia	Anaemia	Splenomegaly	Anthropometric
Burkina Faso (Habluetzel)	No nets	Groups of villages	X		X	X	X		
Cameroon (Moyou-Somo)	No nets	Household			X			X	
Colombia (Kroeger)	Untreated nets	Village		X Pf/Pv^^					
Ecuador (Kroeger)	Untreated nets	Village		X Pf/Pv					
Gambia (D'Alessandro)	Untreated nets	Village	X (X)		X	X	X	X	X
Ghana (Binka)	No nets	Village	X (X)		X	X	X		
Gambia (Snow I)	Untreated nets	Household		X	X	X	X		
Gambia (Snow II)	Untreated nets	Village		X	X	X	X	X	
Iran (Zaim I)	Untreated nets	Village		X Pf/Pv					
Ivory Coast (Henry)	No nets	Village		X	X		X		
Kenya (Nevill)	No nets	Village	X^		X				X
Kenya (Phillips-Howard)	No nets	Village	X	X	X	X	X		X
Kenya (Sexton)	No nets	Household		X					
Madagascar (Rabarison)	Untreated nets	Household		X					
Nicaragua (Kroeger)	No nets	Village		X Pv					
Pakistan (Rowland)	No nets	Household		X Pf/Pv	X Pf/Pv				
Peru Amazon (Kroeger)	Untreated nets	Village		X Pv					
Peru Coast (Kroeger)	Untreated nets	Village		X Pv					
Sierra-Leone (Marbiah)	No nets	Village		X			X	X	

Tanzania (Fraser-Hurt)	No nets	Individual			X		X		
Thailand (Kamol-Ratanakul)	Untreated nets	Household		X Pf/Pv					
Thailand (Luxemburger)	Untreated nets	Individual		X Pf/Pv	X Pf/Pv			X	
		*Randomization by village considered by cluster	**Studies with (X) also measured malaria-specific child mortality ^Also included severe disease	^^Pf = Plasmodium falciparum; Pv = P. vivax. If no detail then Pf					

Additional tables

03 Child mortality from all causes

Study	EIR*	Intervention rate**	Control rate**	Protective efficacy^	Rate difference^
CONTROL GROUPS = NO NETS					
Burkina Faso (Habluetzel)	300 to 500	41.8 (618/14773)	48.7 (688/14118)	14% (-8% to 31%)	6.9 (-2.5 to 16.3)
Ghana (Binka)	100 to 300	28.2 (521/18457)	34.2 (618/18054)	18% (2% to 32%)	6.0 (1.4 to 10.6)
Kenya (Nevill)	10 to 30	9.4 (109/11596)	13.2 (151/11439)	29% (3% to 48%)	3.8 (0.3 to 7.3)
Kenya (Phillips-Howard)	60 to 300	43.9 (782/17833)	51.9 (940/18099)	16% (6% to 25%)	8.1 (3 to 12)
CONTROL GROUP = UNTREATED NETS					
Gambia (D'Alessandro)	1 to 10	18.7 (222/11864)	24.3 (316/12988)	23% (5% to 37%)	5.6 (0.5 to 10.7)
*Transmission intensity (EIR: entomological inoculation rate) **Rates in the intervention and control groups, and the rate difference, are expressed as deaths/1000/year; ages are 1 to 59 months ^95% confidence interval, corrected for design effects					

Additional tables

04 Severe disease

Study	Treated nets	No nets	Relative risk*
Kenya (Nevill)	127/11566	229/11432	0.55 (0.37 to 0.80)
			*95% confidence interval, corrected for design effects

Additional tables

05 Treated nets versus no nets: Prevention of uncomplicated clinical episodes

Study	Treated nets	No nets	Relative risk
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum			
Ivory Coast (Henry)	18/288	42/288	0.43
Kenya (Phillips-Howard)	89/2622	174/2327	0.45
Kenya (Sexton)	44/1747	69/1695	0.62
Sierra Leone (Marbiah)	309/16126	576/15296	0.51
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum			
Pakistan (Rowland)	53/1398	138/1394	0.38
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax			
Nicaragua (Kroeger)	63/2530	212/2730	0.32
Pakistan (Rowland)	182/1398	313/1394	0.58

Additional tables

06 Treated versus untreated nets: Prevention of uncomplicated clinical episodes

Study	Treated nets	Untreated nets	Relative risk
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum			
Gambia (Snow I)	23/3426	34/2912	0.57
Gambia (Snow II)	16/3902	49/3403	0.28
Madagascar (Rabarison)	83/140	110/146	0.61
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum			
Colombia (Kroeger)	53/2295	185/2337	0.29
Iran (Zaim I)	219/4572	78/1935	1.19
Thailand (Kamol-Ratanakul)	15/4410	30/4725	0.54
Thailand (Luxemburger)	33/933	57/939	0.58
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax			
Ecuador (Kroeger)	52/1418	47/1032	0.81
Peru Amazon (Kroeger)	111/2993	149/2716	0.68
Peru Coast (Kroeger)	1066/5552	1702/8199	0.92
Thailand (Kamol-Ratanakul)	13/4410	21/4725	0.66
Thailand (Luxemburger)	35/933	45/939	0.78

Additional tables

07 Summary: Prevention of uncomplicated clinical episodes*

Level stratification	No. trials**	Protective efficacy^
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum		
Control group = no nets	4	50%
Control group = untreated nets	3	39%
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum		
Control group = no nets	1	62%
Control group = untreated nets	4	39%
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax		
Control group = no nets	2	52%
Control group = untreated nets	5	11%
*Summary of results presented in Tables 05 and 06 **For each level, the number of trials contributing to the analysis is indicated ^All results are protective efficacies, that is, (1 - relative risk) x 100, or the percentage reduction in malaria episodes		

Additional tables

08 Treated nets versus no nets: Parasite prevalence (any infection)

Study	Intervention	No nets	Relative risk
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum			
Burkina Faso (Habluetzel)	319/374	361/387	0.43
Cameroon (Moyou-Somo)	54/182	74/179	0.60
Ghana (Binka)	982/1490	1238/1804	0.88
Ivory Coast (Henry)	549/970	624/911	0.83
Kenya (Nevill)	41/241	79/227	0.49
Kenya (Phillips-Howard)	528/978	611/912	0.81
Tanzania (Fraser-Hurt)	29/60	39/60	0.74
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum			
Pakistan (Rowland)	35/956	71/1116	0.58
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax			
Pakistan (Rowland)	92/956	98/1116	1.10

Additional tables

09 Treated versus untreated nets: Parasite prevalence (any infection)

Study	Treated nets	Untreated nets	Relative risk
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum			
Gambia (D'Alessandro)	288/797	280/723	0.93
Gambia (Snow I)	52/145	56/130	0.83
Gambia (Snow II)	58/189	87/233	0.82
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum			
Thailand (Luxemberger)	17/153	16/155	1.08
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax			
Thailand (Luxemberger)	6/153	9/155	0.68

Additional tables

10 Summary: Parasite prevalence*

Level stratification	Number of trials	Protective efficacy^
STABLE MALARIA (entomological inoculation rate > 1): Plasmodium falciparum		
Control group = no nets	7	13%
Control group = untreated nets	3	10%
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium falciparum		
Control group = no nets	1	42%
Control group = untreated nets	1	-8%
UNSTABLE MALARIA (entomological inoculation rate < 1): Plasmodium vivax		
Control group = no nets	1	-10%
Control group = untreated nets	1	32%
*Summary of results presented in Tables 08 and 09 ^Protective efficacy = percentage reduction in malaria episodes		

Additional tables

11 Treated nets versus no nets: High parasitaemia*

Study	Treated nets	No nets	Relative risk
Burkina Faso (Habluetzel)	63/374	86/387	0.76
Kenya (Phillips-Howard)	156/978	210/912	0.69
*Only Plasmodium falciparum in areas of stable malaria			

Additional tables

12 Treated versus untreated nets: High parasitaemia*

Study	Treated nets	Untreated nets	Relative risk
Gambia (D'Alessandro)	94/797	97/723	0.88
Gambia (Snow I)	7/145	13/130	0.48
Gambia (Snow II)	14/189	27/233	0.64
*Only Plasmodium falciparum in areas of stable malaria			

Additional tables

13 Treated nets versus no nets: Anaemia

Study	Treated nets	No nets	WMD*
	Packed cell volume (standard deviation), number of participants	Packed cell volume (standard deviation), number of participants	Packed cell volume
Burkina Faso (Habluetzel)	28.2 (4.5), n = 375	26.7 (3.9), n = 388	1.5
Ghana (Binka)	24.3 (4.7), n = 935	23.1 (5.3), n = 1183	1.2
Ivory Coast (Henry)	32.8 (4.2), n = 83	30.8 (5.2), n = 72	2.0
Kenya (Phillips-Howard)	30.0 (5.1), n = 978	28.5 (4.9), n = 912	1.5
Sierra Leone (Marbiah)	43.4 (22.1), n = 470	38.0 (16.2), n = 450	5.4
Tanzania (Fraser-Hurt)	28.0 (20.1), n = 60	26.5 (19.0), n = 60	1.5
			*WMD: weighted mean difference

Additional tables

14 Treated versus untreated nets: Anaemia

Study	Treated nets	Untreated nets	WMD*
	Packed cell volume (standard deviation), number of participants	Packed cell volume (standard deviation), number of participants	Packed cell volume
Gambia (D'Alessandro)	32.9 (4.6), n = 797	32.6 (4.7), n = 723	0.30
Gambia (Snow I)	34.7 (5.5), n = 145	34.1 (4.3), n = 130	0.60
Gambia (Snow II)	35.8 (12.3), n = 189	33.1 (9.2), n = 233	2.7
			*WMD: weighted mean difference

Additional tables

15 Treated versus no nets: Splenomegaly (Hackett's scale 1 to 5)

Study	Treated nets	No nets	Relative risk
Cameroon (Moyou-S)	60/327	75/268	0.66
Sierra-Leone (Marbiah)	155/470	207/450	0.72

Additional tables

16 Treated versus untreated nets: Splenomegaly (Hackett's scale 1 to 5)

Study	Treated nets	Untreated nets	Relative risk
Gambia (D'Alessandro)	131/797	138/723	0.86
Gambia (Snow II)	40/189	90/233	0.55
Thailand (Luxemberger)	10/148	6/153	1.72

Additional figures

Figure 01

Methodological quality of included trials

Methodological quality of included trials

Trial	Generation of allocation sequence[1]	Allocation concealment[2]	Inclusion of all randomized participants[3]	Blinding[4]
Burkina Faso (Habluetzel)	A	A	A	No
Cameroon (Moyou-Somo)	B	B	A	No
Colombia (Kroeger)	B	B	B	No
Ecuador (Kroeger)	B	B	B	No
Gambia (D'Alessandro)	B	A	A	No
Gambia (Snow I)	B	A	A	Yes[5]
Gambia (Snow II)	B	A	A	Yes[6]
Ghana (Binka)	A	A	A	No
Iran (Zaim I)	B	A	B	No
Ivory Coast (Henry)	A	B	A	No
Kenya (Nevill)	A	A	A	No
Kenya (Phillips-Howard)	A	A	A	No
Kenya (Sexton)	B	A	A	No
Madagascar (Rabarison)	B	A	A	No
Nicaragua (Kroeger)	A	B	B	No
Pakistan (Rowland)	B	A	A	No
Peru Amazon (Kroeger)	B	B	B	No
Peru Coast (Kroeger)	B	B	B	No
Sierra-Leone (Marbiah)	A	A	A	No
Tanzania (Fraser-Hurt)	A	B	A	No
Thailand (Kamol-Ratanakul)	B	B	A	Yes[7]
Thailand (Luxemberger)	A	B	A	Yes[8]

[1] A, adequate, reported using random number tables, computer-generated random numbers, or any other method leading to correct randomization; B, unclear, stated that trial randomized, but method is not described; C, inadequate, if sequences could be related to prognosis

[2] A, adequate, for example, using central randomization; B, unclear, no method reported or the approach was not 'A'; C, inadequate, method is not concealed, for example, using case record numbers

[3] A, losses reported and less than or equal to 10%; B, losses not reported in detail but likely to be below 10%, as assessed from review of all data; C, reported losses greater than 10% or different in both comparison groups

[4] Participant/investigator blinding

[5] For mothers and field staff (but not investigators) by using dilute crystal violet solution as a placebo net treatment)

[6] For villagers and field staff (but not for investigators) by using dilute milk in water solution as a placebo net treatment

[7] For participants and investigators

[8] For families and investigators

Notes

Unpublished CRG notes

Exported from Review Manager 4.2.3
Exported from Review Manager 4.2.2
Exported from Review Manager 4.2.3
Exported from Review Manager 4.2.2
Exported from Review Manager 4.2.1
Short title (no longer in use): Insecticide treated bednets and curtains

Published notes

Amended sections

Cover sheet
Synopsis
Abstract
Background
Objectives
Criteria for considering studies for this review
Search strategy for identification of studies
Methods of the review
Description of studies
Methodological quality of included studies
Results
Discussion
Reviewers' conclusions
Acknowledgements
Potential conflict of interest
References to studies
Other references
Characteristics of included studies
Characteristics of excluded studies
Comparisons, data or analyses
Additional tables and figures

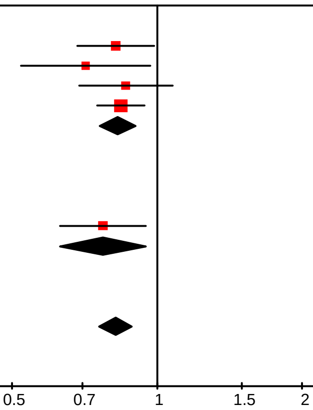
Review: Insecticide-treated bed nets and curtains for preventing malaria

Total number of included studies: 22

Comparison or outcome	Studies	Participants	Statistical method	Effect size
01 Insecticide-treated nets versus all controls				
01 Child mortality from all causes (relative rate)	5	149221	Relative rate (fixed), 95% CI	0.82 [0.76, 0.89]
02 Child mortality from all causes (risk difference)	5	149221	Risk difference (RD) (fixed),	-5.53 [-7.67, -3.39]

Review: Insecticide-treated bed nets and curtains for preventing malaria
Comparison: 01 Insecticide-treated nets versus all controls
Outcome: 01 Child mortality from all causes (relative rate)

Study or sub-category	Treated nets N	Control N	log[Relative rate] (SE)	Relative rate (fixed) 95% CI	Weight %	Relative rate (fixed) 95% CI
01 Controls with no nets						
Ghana (Binka)	18457	18054	-0.1985 (0.0930)		18.61	0.82 [0.68, 0.98]
Kenya (Nevill)	11596	11439	-0.3425 (0.1570)		6.53	0.71 [0.52, 0.97]
Burkina (Habluetzel)	14773	14118	-0.1508 (0.1139)		12.41	0.86 [0.69, 1.08]
Kenya (Phillips-How)	17833	18099	-0.1744 (0.0580)		47.85	0.84 [0.75, 0.94]
Subtotal (95% CI)	62659	61710			85.40	0.83 [0.76, 0.90]
Test for heterogeneity: Chi² = 1.14, df = 3 (P = 0.77), I² = 0%						
Test for overall effect: Z = 4.36 (P < 0.0001)						
02 Controls using untreated nets						
Gambia (D'Alessand)	11864	12988	-0.2600 (0.1050)		14.60	0.77 [0.63, 0.95]
Subtotal (95% CI)	11864	12988			14.60	0.77 [0.63, 0.95]
Test for heterogeneity: not applicable						
Test for overall effect: Z = 2.48 (P = 0.01)						
Total (95% CI)	74523	74698			100.00	0.82 [0.76, 0.89]
Test for heterogeneity: Chi² = 1.53, df = 4 (P = 0.82), I² = 0%						
Test for overall effect: Z = 4.97 (P < 0.00001)						



Review: Insecticide-treated bed nets and curtains for preventing malaria
Comparison: 01 Insecticide-treated nets versus all controls
Outcome: 02 Child mortality from all causes (risk difference)

Study or sub-category	Treated nets N	Control N	Risk difference (RD) (SE)	Risk difference (RD) (fixed) 95% CI	Weight %	Risk difference (RD) (fixed) 95% CI
01 Controls with no nets						
Ghana (Binka)	18457	18054	-6.0000 (2.3300)		21.97	-6.00 [-10.57, -1.43]
Kenya (Nevill)	11596	11439	-3.8000 (1.7900)		37.23	-3.80 [-7.31, -0.29]
Burkina (Habluetzel)	14773	14118	-6.9000 (4.7800)		5.22	-6.90 [-16.27, 2.47]
Kenya (Phillips-How)	17833	18099	-8.1000 (2.5800)		17.92	-8.10 [-13.16, -3.04]
Subtotal (95% CI)	62659	61710			82.35	-5.52 [-7.88, -3.16]
Test for heterogeneity: Chi² = 2.05, df = 3 (P = 0.56), I² = 0%						
Test for overall effect: Z = 4.59 (P < 0.00001)						
02 Controls with untreated nets						
Gambia (D'Alessand)	11864	12988	-5.6000 (2.6000)		17.65	-5.60 [-10.70, -0.50]
Subtotal (95% CI)	11864	12988			17.65	-5.60 [-10.70, -0.50]
Test for heterogeneity: not applicable						
Test for overall effect: Z = 2.15 (P = 0.03)						
Total (95% CI)	74523	74698			100.00	-5.53 [-7.67, -3.39]
Test for heterogeneity: Chi² = 2.05, df = 4 (P = 0.73), I² = 0%						
Test for overall effect: Z = 5.07 (P < 0.00001)